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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
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1. Your reference — PPD 70156/GB/P

30 SEP 2003

2. Patent application number *(The Patent Office will fill in this part)* — 0322917.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SYNGENTA Limited
European Regional Centre
Priestley Road
Surrey Research Park, Guildford,
Surrey, GU2 7YH, United Kingdom

Patents ADP number *(if you know it)* 6254007002 08330748001

If the applicant is a corporate body, give the country/state of its incorporation — UNITED KINGDOM

4. Title of the invention — CHEMICAL PROCESS

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

John Richard WATERMAN
Intellectual Property Department
Syngenta Limited
Jealott's Hill International Research Centre
PO Box 3538
Bracknell, Berkshire, RG42 6YA
UNITED KINGDOM

Patents ADP number *(if you know it)* 06791637002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES (b)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	05
Description	01
Claim(s)	01
Abstract	01
Drawing(s)	00

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Syngenta Limited

Signature M A Rudd Date 30-09-03

Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

Margaret Ann RUDD – 01344 413673

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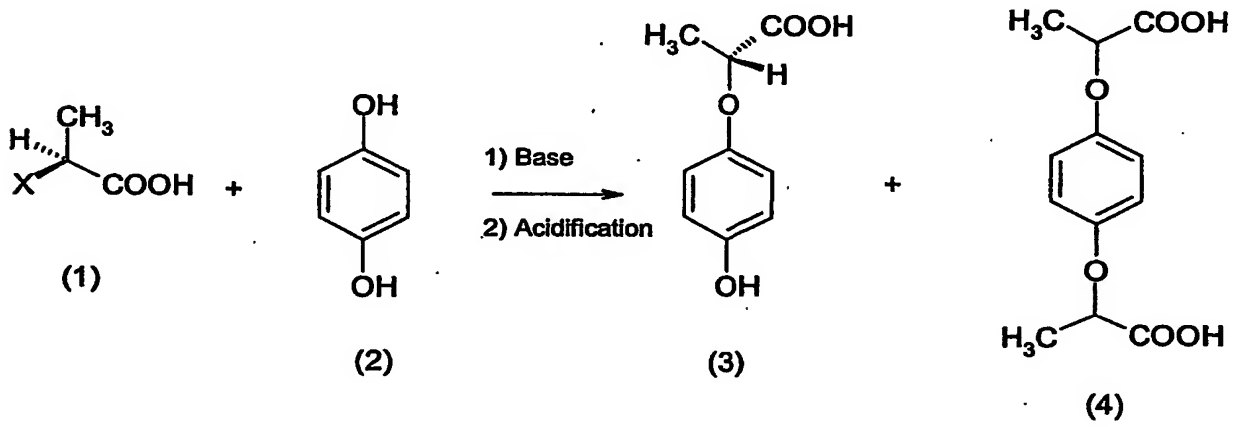
CHEMICAL PROCESS

The present invention relates to a process for the production of optically pure R-hydroxyphenoxypropanoic acid or a salt or ester thereof and its use in making herbicidal products on an industrial scale.

Optically pure R-2-(4-hydroxyphenoxy)propanoic acid (3) can be prepared by the reaction of hydroquinone (2) with an S-2-halopropanoic acid (1) where X is chloro or bromo and is preferably chloro, in the presence of a base.



(1) (2) (3) (4)

The problems associated with producing optically pure R-2-(4-hydroxyphenoxy)propanoic acid from hydroquinone and an S-2-halopropanoic acid are discussed and the relevant prior art is reviewed in EP352168. In particular, over-alkylation of hydroquinone to give the bis-acid (4) and oxidation of hydroquinone to give highly coloured by-products are two serious problems. The solution offered in EP352168 is to perform a complex purification procedure.

On an industrial scale it is desirable to have a simple method for the preparation of R-2-(4-hydroxyphenoxy)propanoic that is essentially free of products of over-alkylation, that is not contaminated by highly coloured by-products and therefore does not require any complex or expensive purification procedures. The applicants have surprisingly found that the use of a mild reducing agent in the manufacture of R-2-(4-hydroxyphenoxy)propanoic acid enables a product to be isolated that meets the above criteria.

There is therefore provided a process for producing R-2-(4-hydroxyphenoxy)propanoic acid by reaction of hydroquinone or a salt thereof with an S-2-halochloropropanoic acid or a salt thereof, in the presence of a mild reducing agent.

In one preferred embodiment excess hydroquinone is recovered for recycle.

It is preferred that isolation of the R-2-(4-hydroxyphenoxy)propanoic acid produced by the reaction is carried out by acidification and filtration.

If necessary or desired the R-2-(4-hydroxyphenoxy)propanoic acid may be converted to a salt or ester thereof by conventional techniques.

The preferred solvents for the reaction are water or water miscible solvents such as methanol or ethanol, alone or in admixture with water.

Preferably the reaction is carried out at a temperature of 10-100°C, more preferably 30-70°C.

The reaction may be carried out at atmospheric pressure or up to 1bar of excess pressure.

It is advantageous to use a deficiency of the S-2-halopropanoic acid, as its salt, in the reaction with hydroquinone, typically 0.25-0.75 mol/mol and preferably 0.3-0.6mol/mol. Preferred salts are alkali metal salts, more preferably the sodium salt.

Suitably an excess of a stoichiometric amount of base on the hydroquinone is used. Preferably the base is used at between 1.5 and 2.5mol/mol on hydroquinone and more preferably at 2-2.2mol/mol.

The mild reducing agent is preferably present throughout the process. It may be added to the process as a solid or as a solution. Incremental additions may be made during the process.

Suitably the mild reducing agent is a neutral or a charged low oxidation state sulphur species, such as sulphur dioxide, a sulphite, a bisulphite, a hydrosulphite, a metabisulphite, a sulphenic acid, a sulphinic acid, for example formamidine sulphinic acid, or a low oxidation state phosphorous species such as a phosphite or hypophosphite, or hydrazine, a hydrazine derivative, or ascorbic acid.

Preferred mild reducing agents are alkali metal sulphite or bisulphite salts such as sodium bisulphite.

The amount of the mild reducing agent used is between 0.01% and 10% by weight on the amount of hydroquinone and is preferably between 0.1% and 5% and most preferably between 0.5% and 2%.

The process is preferably conducted essentially in the absence of oxygen by use of an inert gas blanket, for example nitrogen.

R-2-(4-hydroxyphenoxy)propanoic acid is used in the manufacture of several commercial herbicides such as quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl and fenoxaprop-P-ethyl.

Therefore, in another aspect of the invention there is provided a process for the manufacture of quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl by a) producing R-2-(4-hydroxyphenoxy)propanoic acid by reaction of hydroquinone or a salt thereof with S-2-halochloropropanoic acid or a salt thereof, in the presence of a mild reducing agent, b) reacting the R-2-(4-hydroxyphenoxy)propanoic acid with the appropriate halo-aryl or halo-heteroaryl moiety to give a R-2-((4-aryloxy or heteroaryloxy)phenoxy)propanoic acid and c) esterification of the acid from step b) to give quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl.

The appropriate halo-aryl or halo-heteroaryl moieties are 2-halo-6-chloro-quinoxaline for quizalofop-P-ethyl; 2-halo-3-chloro-5-trifluoromethylpyridine for haloxyfop-P-methyl; 2-halo-5-trifluoromethylpyridine for fluazifop-P-butyl; 2-halo-5-chloro-3-fluoropyridine for clodinafop; 4-halo-3-fluorobenzonitrile for cyhalofop-butyl and 2-halo-6-chloro-benzoxazole for fenoxaprop-P-ethyl where halo is chloro or bromo.

The conversion of R-2-(4-hydroxyphenoxy)propanoic acid to the acids of step b) and and esters of step c) is well known to the skilled person e.g. in Advanced Organic Chemistry, Jerry March, John Wiley & Sons, 1992, p393.

The invention will now be further illustrated with reference to the following Examples.

The product quality was determined by HPLC and the colour was determined as follows. About 1gm of R-2-(4-hydroxyphenoxy)propanoic acid was suspended in 5mls water and adjusted to pH 7 with sodium hydroxide solution before being made up to 10mls with more water. The absorbances of the solution were measured at 420 and 650nm and are expressed as extinctions coefficients (ε, absorbance for a 1molar solution and a 1cm path length.).

Example 1

Preparation of R-2-(4-hydroxyphenoxy)propanoic acid in the presence of sodium bisulphite with recycling of hydroquinone

Step 1

Hydroquinone (574g, 5.22mol) was charged to a reaction flask followed by sodium bisulphite (5.74g) and water (1014g) and a nitrogen blanket was established. The mixture was stirred and heated to 50°C and 47% solution of sodium hydroxide (799.5g, 9.39mol) was added. The solution was heated to 65°C and an aqueous solution of S-2-chloropropanoic acid sodium salt (544.4g, 32.5% as the free acid, 1.63mol) was added. The reaction mixture was held at 65°C for 4 hours. After this period, the total reaction mass weighed 2937.6 g and had a R-2-(4-hydroxyphenoxy)propanoic acid content of 8.60%, equivalent to 252.54product or 85% yield.

700g of water were added and the temperature adjusted to below 45°C. Phosphoric acid (120g) was added to adjust the pH to about 11 and then 98% sulphuric acid (250g) was added to reduce the pH to 6.5-7.5, the temperature being controlled at 55°C during these additions. The solution was then extracted with four successive 638ml portions of methylisobutylketone (MiBK) to give a solution of hydroquinone in MiBK for use in the next cycle.

Step 2.

The MiBK extracts of hydroquinone were then extracted with a solution of sodium hydroxide (687g 47% solution), sodium bisulphite (4.02g) and water (1013g) whilst maintaining an inert atmosphere (nitrogen). The aqueous extract of hydroquinone was charged to a reaction flask followed by fresh hydroquinone (172.2g), 47% sodium hydroxide solution (111.9g) and sodium bisulphite (1.72g), all under a nitrogen blanket. The solution was heated to 65°C and an aqueous solution of S-2-chloropropanoic acid sodium salt (544.4g, 32.5% as the free acid, 1.63mol) was added at this temperature. The reaction mixture was held at 65°C for 4 hours. 700g of water were added and the temperature adjusted to below 45°C. Phosphoric acid (120g) was added to adjust the pH to about 11 and then 98% sulphuric acid (250g) was added to reduce the pH to 6.5-7.5, the temperature being controlled at 55°C during these additions. The un-reacted hydroquinone was removed by extraction with MiBK as above and the residual aqueous phase was then adjusted to pH 2±0.2 using 98% sulphuric acid and extracted with two 250ml portions of MiBK to extract the R-2-(4-hydroxyphenoxy)propanoic acid. The two extracts were combined and washed with a solution of potassium hydroxide (155.5g of 85% strength material) and sodium bisulphite (2.15g) in water (280g).

The aqueous solution of R-2-(4-hydroxyphenoxy)propanoic acid potassium salt was acidified to pH 1 with 32% hydrochloric acid and the temperature adjusted to 20°C. The

slurry was then filtered and the solid product washed with water (one wash 260g and then two washes at 230g). After washing, the product was dried before weighing and analysis.

Weight 188g

Strength 99.4%

Bis acid 0.3%

Yield 63%

Colour Absorbance at 650nm, 0.023, at 420nm, 0.197

The table below gives absorbance data for other reactions

Reaction	Observed color	ε at 650nm	ε at 420nm
Control without any reducing agent	Light brown	0.153	1.614
Addition of 5% sodium bisulphite on hydroquinone	White	0.061	0.243

CLAIMS

1. A process for producing R-2-(4-hydroxyphenoxy)propanoic acid or a salt thereof by reaction of hydroquinone or a salt thereof with S-2-halochloropropanoic acid or a salt thereof in the presence of a mild reducing agent.

2. A process according to Claim 1 wherein the mild reducing agent is a alkali metal sulphite or bisulphite.

3. A process for the manufacture of quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl by a) producing R-2-(4-hydroxyphenoxy)propanoic acid by reaction of hydroquinone or a salt thereof with S-2-halochloropropanoic acid or a salt thereof, in the presence of a mild reducing agent, b) reacting the R-2-(4-hydroxyphenoxy)propanoic acid with the appropriate halo-aryl or halo-heteroaryl moiety to give a R-2-((4-aryloxy or heteroaryloxy)phenoxy)propanoic acid and c) esterification of the acid from step b) to give quizalofop-P-ethyl, haloxyfop-P-methyl, fluazifop-P-butyl, clodinafop, cyhalofop-butyl or fenoxaprop-P-ethyl.

ABSTRACT

CHEMICAL PROCESS

A process for producing optically pure R-hydroxyphenoxypropanoic acid or a salt or ester thereof by reaction of hydroquinone or a salt thereof with an S-halochloropropanoic acid or a salt thereof in the presence of a mild reducing agent.